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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,640	04/08/2004	Wayne M. Coco	3530.1000 US1	8470
38473	7590	08/05/2005	EXAMINER	
ELMORE, CRAIG & VANSTONE, P.C. 209 MAIN STREET N. CHELMSFORD, MA 01863			CHAPPELL, CHERIE M	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 08/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/820,640

Applicant(s)

COCO ET AL.

Examiner

Cherie M. Chappell

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10/20/2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 04/08/2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

HC

DETAILED ACTION

Specification

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Epidermal Growth Factor Agonist

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the protein comprising the amino acid sequence of SEQ ID NO: 2, does not reasonably provide enablement for variants of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims are directed to EGF0021, the protein of SEQ ID NO: 2, or biologically active variants thereof having an amino acid sequence at least 90% identical to the amino acid sequence given in SEQ ID NO: 1. The specification discloses EGF0021 consisting of the acid sequence set forth in SEQ ID NO: 2. The specification further establishes that EGF0021 has biological activity similar to wild type (wt) human (hu) epidermal growth factor (EGF) and provides evidence of a receptor binding assay for this activity. General guidance is given regarding how to make and test variants of any protein.

The scope of the patent protection sought by Applicant as defined by the claim fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein with the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequences are critical to the protein's structure/function

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relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al, 1990, *Science* 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, *Biochemistry* 29:8509-8517; Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, Merz et al., eds, Birkhauser, Boston, pp. 14-16). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein that are tolerant to change (e.g. by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing and screening for active protein variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1-7 are drawn to a polypeptide having at least 90% amino acid identity to SEQ ID NO: 1 having non-specified EGF-like biological activity (defined by Applicant as "one or more activities of the polypeptide of SEQ ID NO: 1"), see specification p. 5, lines 8-10. These claims lack sufficient functional limitation. Applicant states that the biological activity of EGF must be retained by the putative homologous polypeptides but does not indicate whether the entire protein must retain EGF function or whether the activity is measured by the active sites of the protein, the binding sites of the protein, or

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measured by a receptor binding assay. Data from a binding assay of SEQ ID NO: 2 was shown in the drawings (Figures 4A-4C), but it is unclear whether the biological activity associated with SEQ ID NO: 2 refers only to its receptor binding activity or whether another type of biological activity is contemplated by Applicant. Further, Applicant has shown that SEQ ID NO: 2 has the same cell proliferative activity as SEQ ID NO: 1, even when only 1/100 as much was bound to the receptor. However, because of the weak binding activity, there may never be an actual increase in cell proliferation, even if you flood a system with excess SEQ ID NO: 2.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

4. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to amino acid sequences encoding polypeptides having at least 90% sequence identity with SEQ ID NO: 1. The claims also require that the polypeptides possess epidermal growth factor biological activity (see above and specification p. 5, lines 8-10). It is well known in the art that biological activity may be measured by receptor binding assays or several other methodologies. The only evidence in the specification regarding receptor binding activity relates specifically to the protein of SEQ ID NO: 2 (EGF0021) (see Drawings – FIG. 4A-4C).

The claimed subject matter must be described in the specification to ensure that applicant had in his possession, as of the filing of the application, the specific subject matter claimed. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. *In re Glass*, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974).

Additionally, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purpose of the ‘written description’ requirement, whatever is now claimed.” (See p. 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed.” (See *Vas-Cath* at 1116). As discussed above, the skilled artisan cannot envision the detailed amino acid structure of the encompassed homologous polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See, *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 2, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see p. 1115).

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-7 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to amino acid sequences encoding polypeptides having at least 90% sequence identity with SEQ ID NO: 1. The claims also require that the polypeptides possess some degree of epidermal growth factor biological activity (see above and specification p. 5, lines 8-10).

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth

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the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term “epidermal growth factor biological activity” in claims 1-7 is used by the claim to mean “one or more biological activities of epidermal growth factor”, while the accepted meaning encompasses proliferation activity, receptor binding activity, immunogenic activity, etc. The claims do not specify which is intended. The term “epidermal growth factor biological activity” is indefinite because it is not clearly defined.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 1-7 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Coco *et al.*, *Nat Biotechnology*, 2002 Dec;20(12):1246-50. Epub 2002 Nov 11. Coco *et al.* teach an epidermal growth factor polypeptide variant, EGF21, which has enhanced biological activity relative to wild type EGF, as recited in the claims. See p. 1248, top of left column. This variant has virtually the same name as the instantly disclosed variant, EGF0021, which comprises SEQ ID NO: 2 and has the recited activity.

While the reference does not explicitly teach the amino acid sequence of SEQ ID NO: 2, case law has established that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Also, case law has established that a compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Therefore, absent evidence to the contrary, the prior art discloses exactly what is claimed in the instant application.

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Chappell whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 8:30am-7:00pm (EST).

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

CMC

ELIZABETH KEMMERER
PRIMARY EXAMINER